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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LAMBERTSON, DAVID A

ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,855	RASMUSSEN, MICHAEL DOLBERG	
	Examin r	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-20,22,23,59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-20,22,23,59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1, 2, 4, 5, 7-20 and 23 in Paper No. 14 is acknowledged. Upon further consideration and in view of applicant's arguments, claims 59 and 61 are rejoined to Group I.

Claims 1, 2, 4, 5, 7-20, 23, 59 and 61 are pending and under consideration in the instant application.

Priority

Applicant's claim for domestic priority to US Application No. 60/208,052 under 35 U.S.C. 119(e) is acknowledged.

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark on May 24, 2000. It is noted, however, that applicant has not filed a certified copy of the foreign application as required by 35 U.S.C. 119(b). As such, priority is only granted to the date of the provisional application, May 30, 2000.

Information Disclosure Statement

The information disclosure statement filed July 5, 2001 as Paper No. 2 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action.

Claim Objections

Claims 1, 2, 4, 5, 7-20, 22, 23, 59 and 61 are objected to because of the following informalities: "expressable" is misspelled. The correct spelling is "expressible". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 7-20, 22, 23, 59 and 61 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method wherein the integration of amplification units is selected for by reconstitution of a non-functional galactose utilization gene in a bacterial host cell, does not reasonably provide enablement for a method wherein the selection is made by another mechanism in another host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte*

Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is a method of increasing the copy number of a gene of interest in a host cell chromosome, or a method of constructing a host cell thereof, where the gene of interest is contained within an amplification unit. The process by which the amplification unit is introduced into the chromosome requires first making a host cell susceptible to an inhibitory compound that is endogenously produced by the host cell in the presence of a precursor, and then selecting for a chromosomal integration.

Scope of the invention. The scope of the invention is very broad, encompassing a vast number of genes which can be rendered sensitive to an endogenously produced compound, and a vast number of cells which can be modified relative to such a gene. Additionally, in the absence of distinct selection process to determine the integration of the amplification unit into the chromosome of the host cell, the method reads on a vast number of selection processes.

State of the art. The state of the art indicates that a large number of galactose utilization genes are well characterized in bacterial host cells, and that mutation of these genes results in the endogenous production of inhibitory compounds in the presence of galactose precursors and derivatives. However, the state of the art does not clearly set forth other genes that, when mutated, would result in the endogenous production of a compound that would be inhibitory to the mutated cell. Furthermore, the state of the art does not teach a selection process that would not require the reconstitution of the mutant gene to a properly functioning gene. In the absence of such teachings, the skilled artisan would be forced to rely on the instant specification to make and use the instant invention commensurate with the scope that is claimed.

Number of working examples and Guidance provided by applicant. Applicant provides guidance and examples with respect to bacterial cells as it concerns the mutation of genes within the galactose utilization pathway (e.g., *galE*), and that the mutation in a number of these genes results in the cells not being able to properly metabolize galactose, resulting in the production of a compound that is inhibitory to the growth of a cell. Although applicant suggests the use of other cell types (e.g., fungal cells) and other genes to be mutated (e.g., xylose utilization genes), there is no indication that the mutation of these genes or in different host cells results in the endogenous production of a compound that is inhibitory to the host cell. In most instances, the host cell is simply auxotrophic, and cannot utilize the nutritional compound to make a usable biochemical molecule (e.g., a fermentable carbon source or nitrogen source, etc.); this does not equate to the compound being inhibitory by applicant's definition, which requires that the presence of the compound be inhibitory. Furthermore, the only selection process indicated in the instant specification involves the restoration of the non-functional chromosomal gene. In light of the teaches of the instant specification and the prior art, the skilled artisan would not be able to use the invention commensurate with the scope of the claims, which includes non-described selection methods, and host cells and genes which are not known to result in the endogenous production of an inhibitory compound.

Unpredictability of the art and Amount of experimentation required. The claimed invention requires a great deal of unpredictable and undue trial and error experimentation in order to be commensurate with the claimed scope. The skilled artisan would be required to functionally characterize the biological pathways of a vast number of organisms to determine what mutated biological pathways resulted in the endogenous production of an inhibitory compound. The

skilled artisan would have to determine what genes resulted in the production of a compound that was harmful to the growth of an organism, and not simply a gene that was required to produce a compound that was necessary for the growth of an organism. There is a clear distinction between a compound that is necessary for growth and a compound that negatively affects the growth of an organism, and that distinction is made in the instant claims. In the instant specification, applicant teaches that the galactose utilization pathway of bacteria results in the production of an inhibitory compound, and that the restoration of mutants in such genes can be used as a selection process for the integration of amplification units (comprising a gene of interest and a complementary gene for the non-functional mutation) into the chromosome of a host cell. However, the full scope of the claims requires additional undue trial and error experimentation in light of the teachings of the prior art and the instant specification, therefore the invention is not enabled for the entire scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 5, 7-20, 22, 23, 59 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because of the recitation of the limitation "wherein a chromosomally integrated copy of the amplification unit is duplicated or multiplied on the host cell chromosome" as set forth in section d) of the claim. It is unclear how the amplification unit (henceforth AU) duplicates or multiplies by itself following integration. It would seem that the

AU would duplicate regularly with the host chromosome during mitosis given the description of the AU as set forth in the instant specification. It would appear that the claim is meant to read one of the following: 1) the AU is stably integrated into the chromosome, and therefore replicates along with the chromosome during each replication event, 2) multiple integrations of an individual AU occur at a single site of recombination, or 3) that the recombination event results in the introduction of an AU into the chromosome which increases the copy number of the AU in the chromosome by one because the AU is already present in the host genome in at least one copy. Because it cannot be deciphered what the claim language means, the claim is indefinite. In the interest of compact prosecution, the claim is interpreted as it reads for option 3) recited above. This is because the method is drawn to increasing the copy number of an AU in a host chromosome, and since there is no prior discussion of introducing a first AU into the host cell, there must already be one in the chromosome so that the integrated copy increases the copy number of (i.e., multiplies or duplicates) the AU.

Claim 1 is indefinite for its recitation of the limitation "selecting a host cell comprising two or more chromosomally integrated copies of the AU." It is unclear if the method is designed to integrate multiple copies of the AU at one time, or if the selection is meant to include a single integration event into a cell that has already undergone a previous integration event. This is again related to the fact that there is no indication in the claim that a previous integration event had occurred with respect to the AU. Also, it is unclear how the selection for a single integrated copy would differ from a selection for 2 or more integrated copies. Because it cannot be deciphered what the claim language means, the claim is indefinite.

Claim 1 is indefinite as it relates to step f). It would appear that in order to increase the number of integrated copies of the AU in the host cell, one would have to first render a second chromosomal gene non-functional in the host cell, therefore step f) should refer back to step a) as recited in the claimed method. In the very least, step f) should refer back to step c) where a second nucleic acid construct comprising the AU is added, since it is unclear how the AU can arbitrarily increase in copy number without the introduction of a new integrating AU.

Claim 1 recites the limitation "with each repeat" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim. It is unclear what is being referred to as it regards the repeat. It would be remedial to indicate what steps of the method are being referred to by this phrase (e.g., "with each repeat of steps c) through e)," etc.).

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 18 recites the broad recitation "preferably 200 bp, more preferably 300 bp...", and the claim also recites "at least 100 bp" which is the narrower

statement of the range/limitation. The same is true for the recitation of the percent identity limitations, where "70%" is the broad limitation and "preferably 80%, more preferably 90%..." is the narrower statement of the range/limitation.

Regarding claims 17 and 22, the phrase "preferably" (which casts the same meaning as "such as") renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 19 is indefinite because it contradicts a limitation set forth in an independent claim. The independent claim recites that the AU comprises "an expressable [sic] copy of the chromosomal gene" wherein the specification defines an expressable [sic] copy of the gene as one that is functional. Claim 17 then recites that the expressable [sic] copy of the gene is non-functional (see for example page 7, lines 1-8 of the instant specification). It is unclear how the gene can be both functional and non-functional at the same time.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Adams *et al.* (US Patent No. 5,435,730; IDS reference; see entire document; henceforth Adams).

Adams teaches using a host cell that comprises a non-functional gal operon (which includes the *galE* gene) to express a gene of interest by transforming the host cell with a

construct fitting the description of an AU as described on page 13, lines 31-33 of the instant specification (e.g., it contains a gene of interest and an expressible copy of a non-functional conditionally essential gene, and it can be integrated into a host chromosome), such that the construct is integrated into the chromosome of the host cell (see for example column 7, lines 8-26). Significantly, this results in the integration of at least one copy of the gene of interest (i.e., the AU) into the host cell. Furthermore, one of the specific non-functional gene described by Adams is the *galE* gene (see for example column 7, line 17), which is the most preferred embodiment disclosed in the instant application (see for example page 30, lines 10-11 of the instant specification) as being a gene that, when rendered non-functional, renders the cell susceptible to inhibitory compounds. Therefore Adams also teaches the limitation of rendering a cell susceptible to inhibitory compounds. Therefore, Adams anticipates claim 2 of the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 59 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 67 of copending Application No. 09/928,847 (US 2003/0032186; Jorgensen *et al.*; henceforth the '847 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 67 of the '847 application describes a method of using a particular host cell to make a protein, while claim 59 of the instant application describes a similar invention.

The rejection is based on the fact that claim 67 is a process (method of making a protein) that uses a "product-by-process" (the host cell). In essence, the method is drawn to producing a protein using a host cell which comprises at least two copies of a gene of interest, wherein the genes are stably integrated into the chromosome. The process by which the host cell is generated has very little patentable weight because the method is directed to using the cell, not making the cell, and the cell can be made by different methods. The same rationale is true of claim 59 in the '855 patent.

Claim 59 of the instant application recites a method of making a protein using a host cell as described in claim 1 of the same application. Although the specific method of making the host cell in claim 1 of the instant application is not identical to the method of making the host cell as recited in claim 67 of the '847 application, the key element is the host cell that is used, and not the method of making the host cell. In the both the '847 application and the instant case, the host cell is made by complementation of a conditionally essential non-functional gene, whereby the host cell generated comprises at least two copies of a gene of interest in a chromosome (Note: in the instant application, the gene of interest is contained in the AU).

The methods of using the host cell to make a protein in claim 59 of the instant application are obvious in view of claim 67 of the '847 application because the same type of host cell made by a slightly different method can be used to make a protein in claim 67 of the '847 application. One would have been motivated to make a protein by the method of claim 59 because a method of using the same types of cells is claimed by the method of claim 67 in the '847 application. Given the teachings of the copending application and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Also, if both patents are issued and the patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the patent issued from the co-pending '847 application, then two different assignees would hold a patent to the same claimed invention and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 17 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 77 of copending Application No. 09/928,847 (US 2003/0032186; Jorgensen *et al.*; henceforth the '847 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 17 of the instant application describes a method making a particular host cell, while the claim 77 of the '847 application describe a similar invention.

Claim 77 of the '847 application claims a method of making a bacterial host cell comprising at least two copies of a gene of interest stably integrated into the chromosome of a host cell by introducing the gene of interest in the chromosome by complementing a non-functional conditionally essential gene with a corresponding conditionally essential non-functional gene through a recombination event which not only repairs the non-functional gene so that it is functional, but also integrates the gene of interest into the host chromosome. Claim 17 of the instant application describes a similar process, except that there is no indication that the non-functional gene results in the host cell being susceptible to an inhibitory compound. However, the '847 application indicates that in the most preferred embodiment, the conditionally essential gene that is rendered non-functional is *galE* (see for example page 5, line 24 and page 18, lines 23-24 of the '847 application), which must necessarily render the host cell susceptible to an inhibitory compound as it is also the most preferred embodiment of the instant invention (see for example page 20, lines 10-11 of the instant application). Thus the claims are obvious in view of the preferred embodiments set forth in the specification of each respective application.

It would have been obvious to arrive at the instant invention of claim 17 from that of claim 77 in the '847 application because the most preferred embodiments recited in each application are identical as they regard the *galE* gene, which must necessarily result in the same limitations being set forth in each claim. One would have been motivated to combine these teachings because each specification teaches using the *galE* gene as the most preferred embodiment, and one would definitely want to practice the inventions in view of their most preferred embodiments. Given the teachings of the copending application and the level of skill of the ordinary skilled artisan at the time of the applicants' invention, it must be considered that

said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Also, if both patents are issued and the patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the patent issued from the co-pending '847 application, then two different assignees would hold a patent to the same claimed invention and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
July 28, 2003

PATENT EXAMINER
A.U. 1636